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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

usptomailnyc@kslaw.com

Office Action Summary	Application No.	Applicant(s)	
	10/761,498	MICHON ET AL.	
	Examiner	Art Unit	
	S. Devi, Ph.D.	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 February 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-16,18-37 and 39-65* is/are pending in the application.

4a) Of the above claim(s) *6, 7, 29-36, 41-58 and 62-65* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4,5,8,9,11-16,18-28,37,39,40 and 59-61* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

RESPONSE TO APPLICANTS' AMENDMENT

Applicants' Amendments

1) Acknowledgment is made of Applicants' amendments filed 02/19/08 and 11/30/07 in response to the non-final Office Action mailed 05/31/07.

Status of Claims

2) Claim 3, 17 and 38 have been canceled via the amendment filed 11/30/07.

Claims 1, 4-7, 11, 12, 14-16, 18-20, 25-27, 37, 39, 40, 59 and 60 have been amended via the amendment filed 11/30/07.

Claim 39 has been amended via the amendment filed 02/19/08.

Claims 1, 4-16, 18-37 and 39-65 are pending.

Claims 1, 4, 5, 8, 9, 11-16, 18-28, 37, 39, 40 and 59-61 are under examination.

Prior Citation of References

3) The references cited or used as prior art in support of one or more rejections in the instant Office Action and not included on an attached form PTO-892 or form PTO-1449 have been previously cited and made of record.

Objection(s) Withdrawn

4) The objection to the specification made in paragraph 6 of the Office Action mailed 5/31/07 is withdrawn in light of Applicants' amendment to the specification.

5) The objection to claims 1 and 16 made in paragraph 14 of the Office Action mailed 05/31/07 is withdrawn in light of Applicants' amendment to the claims.

Rejection(s) Moot

6) The rejection of claims 3, 17 and 38 made in paragraph 10 of the Office Action mailed 05/31/07 under 35 U.S.C § 112, first paragraph, as being non-enabled with regard to the full scope, is moot in light of Applicants' cancellation of the claims.

7) The rejection of claims 3 and 17 made in paragraph 13(b) of the Office Action mailed 05/31/07 under 35 U.S.C. § 112, second paragraph, as being indefinite, is moot in light of Applicants' cancellation of the claims.

8) The rejection of claims 3, 17 and 38 made in paragraph 13(i) of the Office Action mailed

05/31/07 under 35 U.S.C. § 112, second paragraph, as being indefinite, is moot in light of Applicants' cancellation of the claims.

Rejection(s) Withdrawn

9) The rejection of claims 1, 16, 59, 60 and those dependent therefrom made in paragraph 7 of the Office Action mailed 05/31/07 under 35 U.S.C. § 112, first paragraph, as containing new matter, is withdrawn in light of Applicants' amendment to the claims.

10) The rejection of claim 37 and those that depend therefrom made in paragraph 8 of the Office Action mailed 05/31/07 under 35 U.S.C. § 112, first paragraph, as containing new matter, is withdrawn in light of Applicants' amendment to the specification. A new rejection is set forth below to reject the claim as amended currently.

11) The rejection of claims 18 and 20 made in paragraph 9 of the Office Action mailed 05/31/07 under 35 U.S.C § 112, first paragraph, as being non-enabled, is withdrawn.

12) The rejection of claims 1, 14 and 16 made in paragraph 13(a) of the Office Action mailed 05/31/07 under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claims.

13) The rejection of claims 1, 4-9, 11-16, 18-28, 37, 39, 40 and 59-61 made in paragraph 10 of the Office Action mailed 05/31/07 under 35 U.S.C § 112, first paragraph, as being non-enabled with regard to the full scope, is withdrawn in light of Applicants' amendment to the claims and/or the base claim(s). A new rejection is set forth below that addresses the claims as amended. Applicants' arguments have been addressed therein to the extent applicable to the amended claims.

14) The rejection of claims 25 and 40 made in paragraph 11 of the Office Action mailed 05/31/07 under 35 U.S.C § 112, first paragraph, as being non-enabled, is withdrawn in light of Applicants' amendment to the base claim(s). A new rejection is set forth below that addresses the claims as amended. Applicants' arguments have been addressed therein to the extent applicable to the rejection of the amended claims.

15) The rejection of claims 1, 4, 5, 11, 12, 15 and 37 made in paragraph 13(b) of the Office Action mailed 05/31/07 under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claims.

16) The rejection of claims 37 and 40 made in paragraph 13(c) of the Office Action mailed 05/31/07 under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claims.

17) The rejection of claims 25 and 40 made in paragraph 13(d) of the Office Action mailed 05/31/07 under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claims.

18) The rejection of claims 1 and 16 made in paragraph 13(e) of the Office Action mailed 05/31/07 under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claims.

19) The rejection of claims 26 and 27 made in paragraph 13(f) of the Office Action mailed 05/31/07 under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claims.

20) The rejection of claim 16 made in paragraph 13(g) of the Office Action mailed 05/31/07 under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claim.

21) The rejection of claim 26 made in paragraph 13(h) of the Office Action mailed 05/31/07 under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claim.

22) The rejection of claims 4, 5, 8, 9, 11-15, 18-28, 37, 39, 40 and 59-61 made in paragraph 13(i) of the Office Action mailed 05/31/07 under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the base claim.

New Rejection(s) Necessitated by Applicants' Amendment

Rejection(s) under 35 U.S.C. § 112, First Paragraph (New Matter)

23) Claim 1 and the dependent claims 4, 5, 8, 9, 11-15, and claim 16 and the dependent claims 18-28, 37, 39, 40 and 59-61 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claim 1, as amended, includes the limitation: 'wherein said de-N-acetylated polysaccharide or said de-N-acetylated oligosaccharide is derived from bacterial, yeast or cancer cell surface or capsular polysaccharide or oligosaccharide, naturally or synthetically obtained'. The conjugate claimed in the amended claim 1 comprises a de-N-acetylated polysaccharide or a de-N-acetylated oligosaccharide covalently attached to protein *without* N-acryloylation. Applicants state that the support for this amendment is found on page 5, line 20 to page 6, line 32 of the specification. While the fourth paragraph under 'Summary of the Invention' describes capsular and cell surface 'polysaccharides' extracted from bacterial, yeast, or mammalian cell supernatants, or directly from bacterial, yeast or mammalian cells, there is no descriptive support a polysaccharide-protein conjugate or an oligosaccharide-protein conjugate as claimed wherein 'a de-N-acetylated polysaccharide or a de-N-acetylated oligosaccharide is derived from bacterial, yeast or cancer cell surface' as recited currently, wherein the de-N-acetylated polysaccharide or a de-N-acetylated oligosaccharide is covalently attached to protein via a beta-propionamido linkage wherein the conjugate elicits protective antibodies reactive with the polysaccharide or the oligosaccharide as claimed in the amended claim 1. Similarly, the limitation in the amended claim 16 'de-N-acetylating a bacterial, yeast or cancer cell surface or capsular' polysaccharide or oligosaccharide, 'naturally or synthetically obtained by at least 50% ..... wherein the polysaccharide-protein conjugate or the oligosaccharide-protein conjugate elicits protective antibodies reactive with the polysaccharide or the oligosaccharide'. Applicants state that the support for the limitation 'the polysaccharide-protein conjugate or the oligosaccharide-protein conjugate elicits protective antibodies reactive with the polysaccharide or the oligosaccharide' is found at lines 2-6 of page 12 of the specification, which is reproduced below:

> This invention is also directed to vaccine preparations. According to this invention, the isolated 13-propionamido-linked polysaccharide-protein conjugates described above may be used as an antigen to generate antibodies that. are reactive against the polysaccharide or oligosaccharide and hence reactive against the organism or cell from which the polysaccharide or oligosaccharide was isolated. The vaccines

This part of the specification however provides no descriptive support for any 'protective antibodies' reactive with the polysaccharide or the oligosaccharide whether or not derived from a bacterial yeast or cancer cell surface. Furthermore, the now recited 'capsular' polysaccharide or oligosaccharide, 'naturally or synthetically obtained' encompasses a plethora of generic naturally or synthetically obtained capsular polysaccharides or oligosaccharides of any source other than bacterial, yeast or

cancer cell source and is required, as the recited conjugate, to elicit 'protective antibodies' reactive with the polysaccharide or the oligosaccharide. There is no support for the limitations of such enormous scope. A step that comprises de-N-acetylating bacterial cell surface, yeast cell surface or cancer cell surface lacks descriptive support. Therefore, the above-identified limitations in the claims are considered to be new matter. *In re Rasmussen*, 650 F2d 1212 (CCPA, 1981). New matter includes not only the addition of wholly unsupported subject matter but also, adding specific percentages or compounds after a broader original disclosure, or even omission of a step from a method. See M.P.E.P 608.04 to 608.04(c).

Applicants are invited to point to specific line and page numbers of the specification, as originally filed, that provide descriptive support for the limitations identified above, or alternatively, remove the new matter from the claims. Applicants should specifically point out the support for any amendment made to the disclosure. See MPEP 714.02 and 2163.06.

24) Claim 14 is rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claim 14, as amended, includes the limitation: 'β-propionamido linkage comprises a 'β-carbon attached to: (a) a side-chain nitrogen of the lysine residue of the protein; or (2) a sulfur of the' cysteine residue of the protein. Applicants state that support for this amendment is found in Figure 1 and lines 3-5 of page 10 of the specification. However, these parts of the specification do not provide descriptive support for the now added β-carbon and its specific attachments. Therefore, the above-identified limitations in the claim are considered to be new matter. *In re Rasmussen*, 650 F2d 1212 (CCPA, 1981). New matter includes not only the addition of wholly unsupported subject matter but also, adding specific percentages or compounds after a broader original disclosure, or even omission of a step from a method. See M.P.E.P 608.04 to 608.04(c).

Applicants are invited to point to specific line and page numbers of the specification, as originally filed, that provide descriptive support for the limitations identified above, or alternatively, remove the new matter from the claim. Applicants should specifically point out the support for any amendment made to the disclosure. See MPEP 714.02 and 2163.06.

25) Claim 59 is rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claim 59, as amended, includes the new limitations: 'β-propionamido linkage is formed .....and reacting an acryloyl moiety of the N-acryloylated polysaccharide or the N-acryloylated oligosaccharide with the protein, wherein the degree of .....'. Applicants state that the support for this amendment can be found at page 8, line 24 to page 9, line 7 of the originally filed specification. However, this part of the specification does not describe reacting 'an an acryloyl moiety' as recited in the claim. Therefore, the above-identified limitations in the claim are considered to be new matter. *In re Rasmussen*, 650 F2d 1212 (CCPA, 1981). New matter includes not only the addition of wholly unsupported subject matter but also, adding specific percentages or compounds after a broader original disclosure, or even omission of a step from a method. See M.P.E.P 608.04 to 608.04(c).

Applicants are invited to point to specific line and page numbers of the specification, as originally filed, that provide descriptive support for the limitations identified above, or alternatively, remove the new matter from the claim. Applicants should specifically point out the support for any amendments made to the disclosure. See MPEP 714.02 and 2163.06.

26) Claim 37 and the dependent claim 39 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claim 37, as amended, includes the limitations: 'protective immunity against at least one member of a genus of an organism from which the polysaccharide or the oligosaccharide was obtained'. Applicants state that support can be found at lines 29-31 of page 4; lines 22-25 of page 11 and lines 1-17 of page 12 of the specification, which have been reproduced below in that order:

> An aspect of the invention is a method of eliciting the production of antibodies in mammals using the β-propionamido-linked polysaccharide-protein conjugates that protect the mammals against infection or disease.
>
> polysaccharide. Another advantage of this method over the prior art is that the polysaccharide or oligosaccharide is not altered at a charged functional group which often interact with/or form part of the epitope crucial for immunity.
>
> **C. Vaccines**

> This invention is also directed to vaccine preparations. According to this invention, the isolated 13-propionamido-linked polysaccharide-protein conjugates described above may be used as an antigen to generate antibodies that. are reactive against the polysaccharide or oligosaccharide and hence reactive against the organism or cell from which the polysaccharide or oligosaccharide was isolated. The vaccines of the present invention may be a combination or multi component vaccine further comprising in combination with the 13-propionamido-linked polysaccharide-protein conjugate other components, including but not limited to Diphtheria-Tetanus-Pertusis (DTP), Tetanus-Diphtheria (Td), DTaP, a DTaP-Hib vaccine, a DTaP-IPV-Hib vaccine, and the like and combinations thereof, to provide a multifunctional vaccine useful in immunizing against a variety of diseases causing organisms or disease causing cells.
>
> The vaccines of this invention may provide active or passive immunity. Vaccines for providing active immunity comprise an isolated and purified N-acryloylated polysaccharide or oligosaccharide conjugated to at least one antigenic peptide.

However, there is no inherent or implicit descriptive support in these parts of the specification, as originally filed, for protective immunity against *at least one member of a genus of an organism from which the polysaccharide or the oligosaccharide was obtained*. Therefore, the above-identified limitations in the claims are considered to be new matter. *In re Rasmussen*, 650 F2d 1212 (CCPA, 1981). New matter includes not only the addition of wholly unsupported subject matter but also, adding specific percentages or compounds after a broader original disclosure, or even omission of a step from a method. See M.P.E.P 608.04 to 608.04(c).

Applicants are invited to point to specific line and page numbers of the specification, as originally filed, that provide descriptive support for the limitations identified above, or alternatively, remove the new matter from the claim. Applicants should specifically point out the support for any amendment made to the disclosure. See MPEP 714.02 and 2163.06.

Rejection(s) under 35 U.S.C. § 112, First Paragraph (Scope of Enablement)

27) Claims 1, 4, 8, 9, 11-16, 18-28, 37, 39, 40 and 59-61 are rejected under 35 U.S.C § 112, first paragraph, because the specification, while being enabling for a conjugate comprising, for example, an N-acryloylated group B streptococcus type III (GBS III) polysaccharide directly conjugated at the beta position to tetanus toxoid (wherein the percent N-acryloylation of the polysaccharide is undisclosed), and a pharmaceutical composition comprising the same, said composition capable of inducing a homologous type III polysaccharide-specific opsonophagocytic antibody response, does not reasonably provide enablement for such a conjugate or composition comprising N-acryloylated GBS III polysaccharide-TT or N-acryloylated GBS III oligosaccharide-TT, or GBS type Ia, Ib, II, V, or VIII polysaccharide- or oligosaccharide-protein carrier conjugate, or any N-acryloylated bacterial polysaccharide or N- acryloylated oligosaccharide similarly conjugated to a TT or non-TT

protein carrier and capable of providing 'protective antibodies' reactive with the polysaccharide or the oligosaccharide of a non-homologous strain or type of GBS III, or any other bacteria, yeast, cancer cell surface from which the de-N-acetylated polysaccharide- or the de-N-acetylated oligosaccharide component of the conjugate was obtained, or the naturally or synthetically obtained capsular polysaccharide or oligosaccharide, as broadly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most clearly connected, to make and/or use the invention commensurate in scope with these claims.

Instant claims are evaluated based on the Wands factors. Many of the factors regarding undue experimentation have been summarized in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Circ. 1988) as follows:

- The quantity of experimentation necessary (time and expense);
- The amount of direction or guidance presented;
- The presence or absence of working examples of the invention;
- The nature of the invention;
- The state of the art;
- The relative skill of those in the art; and
- The breadth of the claims.

In the instant case, claims 1 and 16, as amended, broadly encompass a conjugate that 'elicits protective antibodies reactive with the polysaccharide or the oligosaccharide', i.e., protective antibodies against any bacterial disease or condition including Group B streptococcal infection, cancer, or yeast infections. A myriad of pathogenic bacteria, and any number of serogroups, serotypes, or species of *Streptococcus,* and any types of Group B *Streptococci* are encompassed within the scope of the claims against which the claimed polysaccharide- or oligosaccharide-protein conjugate vaccine is required to elicit 'protective antibodies reactive with the polysaccharide or the oligosaccharide'. The conjugate claimed in the amended claim 1 comprises a de-N-acetylated polysaccharide or a de-N-acetylated oligosaccharide derived from bacterial, yeast or cancer cell surface or naturally or synthetically obtained capsular polysaccharide or oligosaccharide covalently attached to protein without N-acryloylation. Claims 37 and 39-40 depend directly or indirectly from claim 1 or 16. The limitation 'Streptococcus' encompasses multiple species, such as, *Streptococcus pyogenes*, *Streptococcus mutans*, *Streptococcus faecalis, Streptococcus pneumoniae* etc. Both homologous and heterologous strains or types of Group B *Streptococci* are encompassed within the limitation 'at least one member of a genus of an organism from which the polysaccharide or

oligosaccharide .... was obtained' and within the limitation '*Streptococcus*'. The limitation 'organism' in the dependent claim 37 is broader in scope than the term bacteria, yeast, or cancer cell. The term 'oligosaccharide' encompasses oligosaccharides obtained from lipopolysaccharides, capsular polysaccharides, a cell wall polysaccharides, exopolysaccharides etc. The protective ability of a lipopolysaccharide, cell wall polysaccharide, capsular polysaccharide, or exopolysaccharide of at least one member of 'a genus of an organism' from which the polysaccharide or oligosaccharide .... was obtained', or the protective ability of a cell wall polysaccharide, capsular polysaccharide, or exopolysaccharide of any strain, serogroup, serotype, or type of *Streptococcus,* in a de-N-acetylated conjugated form or de-N-acetylated, N-acryloylated and conjugated form is not predictable absent a concrete showing. The data provided for a *Streptococcus* species in Table 6 are limited to a showing that the de-N-acetylated and N-acryloylated group B *Streptococcus* type III capsular polysaccharide conjugated to tetanus toxoid by Michael addition, on administration along with alum to laboratory animals, elicited homologous GBS type III capsular polysaccharide-specific opsonophagocytic antibody response as measured on day 52 post immunization. There is no evidence that this conjugate would induce anti-capsular polysaccharide opsonophagocytic antibodies that would protect against any other strains, serogroups, serotypes, or types of '*Streptococcus*' other than the homologous strain of group B *Streptococcus* type III. This is important because, by and large, the opsonophagocytic GBS anti-capsular polysaccharide antibodies induced by a conjugate vaccine comprising the corresponding polysaccharide or oligosaccharide are strain- or type-specific. Applicants assert that lines 29-31 of page 15 of the specification state that the polysaccharide used with the instant invention may induce antibody which is cross-reactive with other pathogenic organisms and thus have the ability in protecting against infection by these other bacteria. Applicants submit the reference of Ota *et al. Infect. Immun.* 55: 266-268, 1987 and state that such cross-reactive polysaccharides can be easily determined by those of ordinary skill in the art without any undue experimentation. However, the cross-reactive polysaccharides are not the same as 'cross-protective' polysaccharides. There is no predictability that generic cross-reactive polysaccharides, once subject to the instant conjugation process, would retain their protective or cross-protective epitopes. An *E. coli* O111 O-specific oligosaccharide conjugate would not be expected to elicit protective antibodies against another strain or O-type of the same bacterium, for example *E. coli* serotype O157. From what is known in the art about the polysaccharide-specific opsonophagocytic response against a

particular bacterial pathogen, or a particular serogroup, serotype, or capsular type of a particular bacterial pathogen, it is unlikely that a GBS III capsular polysaccharide-TT conjugate produced according to the instant invention would induce antibodies that are 'protective' against heterologous *Streptococci*, for example, Group C streptococci, or heterologous type Ia, Ib, II, V, VIII, or a combination thereof. Neither there is evidence, nor is it predictable that a non-capsular polysaccharide, for example, of GBS III when conjugated as described in the instant application, would elicit 'protective antibodies' to *Streptococci* of heterologous capsular types, absent a concrete showing. Therefore, considerable amount of undue experimentation would have been required by one of skill in the art at the time the invention was made to practice the full scope of the invention due to the lack of evidence/guidance within the instant specification, the lack of working examples enabling the full scope of the claimed invention, the unpredictability factor, the breadth of the claims, and the quantity of experimentation necessary.

Rejection(s) under 35 U.S.C. § 112, First Paragraph (Lack of Enablement)

28) Claims 25 and 40 are rejected under 35 U.S.C § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The instant claims are evaluated based on the *Wands* analysis. Many of the factors regarding undue experimentation have been summarized in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Circ. 1988) as follows:

- The quantity of experimentation necessary (time and expense);
- The amount of direction or guidance presented;
- The presence or absence of working examples of the invention;
- The nature of the invention;
- The state of the art;
- The relative skill of those in the art;
- The predictability or unpredictability of the art; and
- The breadth of the claims.

- In the instant case, the nature of the invention is related to a combination vaccine or a combination pharmaceutical composition comprising: (a) a pharmaceutically acceptable carrier; (b) a polysaccharide-protein conjugate or an oligosaccharide-protein conjugate comprising a de-N-acetylated polysaccharide or oligosaccharide covalently attached to protein via beta-propionamido linkage, or a polysaccharide-protein conjugate or an oligosaccharide-protein conjugate comprising an

N-acryloylated polysaccharide or oligosaccharide conjugated to a bacterial protein via a lysine or a cysteine residue wherein the conjugate elicits 'protective antibodies' reactive with the polysaccharide or the oligosaccharide, as claimed in claims 1 and 16; and (c) a second immunogen component selected from the group consisting of DTP, DTaP, tetanus-diphtheria, DTaP-Hib, DtaP-IPV-Hib, and combinations thereof. The elected polysaccharide or oligosaccharide is the *Streptococcus* Group B polysaccharide or oligosaccharide species; DTaP second immunogenic component species; and tetanus toxoid protein species. This means that the claimed vaccine or composition comprising the de-N-acetylated or N-acryloylated *Streptococcus* Group B polysaccharide or oligosaccharide conjugated to tetanus toxoid and further comprising the DTaP second immunogenic component or a combination second immunogenic component that comprises the DTaP is *required* to elicit 'protective antibodies' reactive with the *Streptococcus* Group B polysaccharide or the *Streptococcus* Group B oligosaccharide or the *Streptococcus* Group B de-N-acetylated polysaccharide or the de-N-acetylated *Streptococcus* Group B oligosaccharide. However, there is a lack of showing that a de-N-acetylated or an N-acryloylated *Streptococcus* Group B polysaccharide- or oligosaccharide-tetanus toxoid conjugate as claimed in the instant invention can be combined with a second monovalent or multivalent protein component, such as, DTaP, or DTP, Td, DTap-Hib, DTaP-IPV-Hib, or combinations thereof, wherein the conjugate still produces the required 'protective antibodies'. There is no showing that the instantly claimed conjugate when combined with one or more of any of the recited second component or combinations thereof, would retain its 'protective' immunogenic function as a vaccine and would effectively elicit an optimally 'protective' GBS polysaccharide- or GBS oligosaccharide-specific immune response. This is important because the state of the art on combination vaccines at the time of the invention indicated the occurrence of potential interference by one or more added vaccine components. For instance, Barington *et al.* (*Infect. Immun.* 61: 432-438, 1993 – Applicants' IDS) taught that immunizations of conjugated polysaccharides and unconjugated (free) carrier protein (for example, TT in the instant case), lead to a non-epitope specific suppression of the antibody response not only to the carrier protein, but the polysaccharide as well. Corbel (*Biologicals* 22: 353-360, 1994 – Applicants' IDS) taught that the use of diphtheria and tetanus proteins as carriers for multiple polysaccharide conjugates may lead to epitope suppression of anti-polysaccharide responses (see abstract). Most importantly, the combining of DTaP and IPV or DTaP and IPV with a bacterial capsular polysaccharide-protein conjugate has been shown in the art

to result in interference and a significant and pronounced reduction in immune response to IPV. For example, see page 1688 of Eskola *et al.* (*Lancet* 348: 1688-1692, 1996), who concluded that '[t]he immunogenicity of all antigens must be tested before new combinations can be accepted for vaccination programmes …'. Applicants submit that the Eskola reference shows that Hib antibodies were obtained when DTP-a was administered in combination with Hib capsular polysaccharide. However, Eskola *et al.* used a conjugate produced by a method non-identical to Applicants' method and concluded that '[a]lthough all combinations proved safe, the poor immunogenicity of the Hib component when it was mixed with DTP-a in the two dose schedules studied here raises important questions about the immunonological mechanism of the interference seen and about its clinical relevance'. See first paragraph under 'Discussion'. In the instant case, Applicants claim that their claimed conjugate or vaccine is novel which uses a novel method of conjugation. However, it is neither shown within the instant specification, nor is it predictable that the instantly claimed GBS conjugate species comprising the beta-propionamido linkage when combined with a preparation containing DTaP or Hib conjugate, i.e., DTap-Hib or DTaP-IPV-Hib, or a combination thereof, would not produce interference or an immune response-suppressing effect on one or more vaccine components, but would retain its ability to elicit 'protective antibodies' reactive with the polysaccharide or the oligosaccharide or the de-N-acetylated polysaccharide or the de-N-acetylated oligosaccharide. Corbel further taught that the formulation of the combinations may present specific problems resulting from the interaction of the various components with each other and with the adjuvants and excipients (see page 353). It is noted that Applicants have not advanced any arguments with regard to the cited disclosure of Barington *et al.* and Corbel. Given the lack of evidence/guidance, the teachings in the state of the art on the potential interference by one or more added vaccine components, poor polysaccharide immunogenicity, and the suppression of antibody response to the polysaccharide or the carrier protein, the unpredictability factor, the breadth of the claims, the lack of working examples, and the quantity of experimentation necessary, undue experimentation would have been required by one of ordinary skill in the art to practice the invention as claimed.

Rejection(s) under 35 U.S.C. § 112, Second Paragraph

29) The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> The specification shall conclude one or more claims particularly pointing out and distinctly claiming the subject matter which the Applicant regards as his/her invention.

30) Claims 1, 4, 5, 8-16, 18-28, 37, 39, 40 and 59-61 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite, for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

(a) Claim 1 is indefinite and confusing in the limitation: 'wherein said de-N-acetylated polysaccharide or said de-N-acetylated oligosaccharide is derived from bacterial, yeast or cancer cell surface'. Does it mean that the recited bacterial, yeast or cancer cell surface contain a native de-N-acetylated polysaccharide or native de-N-acetylated oligosaccharide, which is derived directly from said cell surface?

(b) Claims 1 and 16 are confusing and appear to have improper antecedent basis in the limitation: 'the polysaccharide' (see line 9 of claim 1 and last line of claim 16), because it is unclear where exactly does the antecedence come from for the limitation 'polysaccharide'. The earlier part of the claim includes the limitations of a 'de-N-acetylated polysaccharide' and 'capsular polysaccharide'. Is 'the polysaccharide' recited in line 9 of claim 1 the capsular polysaccharide or the de-N-acetylated polysaccharide?

(c) Analogous rejection and criticism apply to claims 4, 5, 11, 12 and 15 with regard to the limitation: 'the polysaccharide'.

(d) Claim 16 is vague and indefinite in the limitation: reacting the N-acryloylated polysaccharide or the N-acryloylated oligosaccharide with protein 'to form a β-propionamido linkage'. Does the reacting step result in the conjugate or the recited linkage?

(e) Claim 26 is indefinite because it is broadening in scope in the limitation: 'elicits an immune response specific to the polysaccharide or the oligosaccharide'. Claim 26 depends from claim 1 or claim 16, which are drawn to a polysaccharide-protein or an oligosaccharide-protein conjugate that elicits 'protective antibodies reactive with the polysaccharide or the oligosaccharide'. Does the immune response recited in the dependent claim 26 include a non-protective immune response?

(f) Claim 37, which depends from the amended claim 1 or 16, is indefinite, confusing and improperly broadening in scope in the limitation: 'member of a genus of an organism from which the polysaccharide or the oligosaccharide was obtained'. Claim 1 from which claim 37

depends recites that the de-N-acetylated polysaccharide or the de-N-acetylated oligosaccharide is derived from bacterial, yeast or cancer cell surface, or naturally or synthetically obtained capsular polysaccharide or oligosaccharide. Claim 16 from which claim 37 depends recites that capsular polysaccharide or oligosaccharide is naturally or synthetically obtained and that a de-N-acetylated polysaccharide or a de-N-acetylated oligosaccharide is formed by de-N-acetylating a bacterial, yeast or cancer cell surface by at least 50%. What is precisely encompassed within the scope of the limitation 'member of a genus of an organism from which the polysaccharide or the oligosaccharide was obtained' is unclear. Is a human having a cancer cell a member of a 'genus of an organism'?

(g) Claim 39 has improper antecedent basis in the limitation: 'the bacteria'. Claim 39 depends directly from claim 37 and indirectly from claim 1 or 16, which does not include the recitation of any 'bacteria'.

(h) Claim 60 is grammatically incorrect in the limitation: 'oligosacchride N-acryloylated by at least 95%'.

(i) Claims 4, 5, 8-15, 18-28, 37, 39, 40 and 59-61, which depend from claim 1 or 16, are also rejected as being indefinite because of the indefiniteness identified above in the base claim.

Objection(s) to Claim(s)

31) Claims 1 and 16 are objected to for the following reasons:

(a) Claim 1 is objected to for lacking a preceding article before the limitations: 'protein' (see line 4), 'bacterial protein' (see line 11), and 'synthetic protein' (see line 11).

(b) Claim 16 is objected to for lacking a preceding article before the limitation: 'protein' (see part C), 'bacterial protein' (see line 11), and 'synthetic protein' (see line 11).

Remarks

32) Claims 1, 4, 5, 8, 9, 11-16, 18-28, 37, 39, 40 and 59-61 stand rejected.

33) Applicants' amendment necessitated the new ground(s) of rejection presented in this Office action. **THIS ACTION IS MADE FINAL.** Applicants are reminded of the extension of time policy as set forth in 37 C.F.R 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the

THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 C.F.R 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

34) Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. The Fax number for submission of amendments, responses and/or papers is (571) 273-8300, which receives transmissions 24 hours a day and 7 days a week.

35) Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAG or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.Mov. Should you have questions on access to the Private PAA system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (in USA or CANADA) or 571-272-1000.

36) Any inquiry concerning this communication or earlier communications from the Examiner should be directed to S. Devi, Ph.D., whose telephone number is (571) 272-0854. A message may be left on the Examiner's voice mail system. The Examiner can normally be reached on Monday to Friday from 7.15 a.m. to 4.15 p.m. except one day each bi-week, which would be disclosed on the Examiner's voice mail system.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Shanon Foley, can be reached on (571) 272-0898.

/S. Devi/
S. Devi, Ph.D.
Primary Examiner
AU 1645

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